REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

Claims 14-22 and 42-49 are currently pending. Claim 14 is amended herein to recite, in new step (iv), that the sorting step is repeated on the single stranded nucleic acids isolated in step (h). Support for this amendment may be found throughout the specification and claims as-filed, especially on page 5, lines 8-10 and page 8, lines 12-17. Claim 14 has also been amended to recite "sorting" instead of "categorizing". Basis for this amendment may be found on page 1, lines 1-3, of the specification. No prohibited new matter has been introduced by this Amendment. Applicants reserve the right to pursue in a division or continuation application any subject matter canceled by way of this Amendment without prejudice or disclaimer.

REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 14-22, 42-46, 49 stand rejected under 35 U.S.C. 103(a) as being purportedly unpatentable over Rothberg *et al.* (U.S. Patent 5,871,697) in view of Dynal Catalog (1995) and further in view of Van Ness *et al.* (U.S. Patent 5,667,976).

Claims 47-48 stand rejected under 35 U.S.C. §103(a) as being purportedly unpatentable over Rothberg et al. (U.S. Patent 5,871,697 or Rothberg et al.) in view of Dynal Catalog (1995) and further view of Van Ness et al. (U.S. Patent 5,667,976) as

applied to Claims 14-22, 42-46, 49, and further in view of Hartley et al (U.S. Patent 5,106,727).

Rothberg *et al.* is cited for purportedly disclosing a method for categorizing nucleic acid by: (i) digesting double-stranded nucleic acid with an endonuclease to produce a nucleic acid population, wherein the endonuclease is selected such that each nucleic acid in the resulting nucleic acid population has sticky ends of a known base sequence and of a known common length; (ii) contacting the nucleic acid population with an adaptor to ligate the adaptor to a termini of each nucleic acid in the population such that the adaptor has a double stranded primer portion having a known base sequence and a single stranded portion complementary to the know sticky end of the nucleic acids of the population; (iii) contacting the nucleic acid with one or more oligonucleotide sets and (iv) categorizing the nucleic acid by isolating nucleic acid which correctly hybridizes to an oligonucleotide set, wherein each oligonucleotide sequence in each oligonucleotide set has a pre-determined recognition sequence such that the recognition sequence is situated in the portion of the nucleic acid which was double stranded after digestion with the endonuclease.

Dynal is cited for purportedly disclosing a method of generating and isolating non-immobilized single-stranded nucleic acid. Van Ness is cited for purportedly disclosing that covalently immobilized capture nucleic acid sequences have certain improved properties over non-covalently attached capture nucleic acids. Hartley is cited for purportedly disclosing non-standard bases.

To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re* Dow Chemical Co., . . . 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the cited references, alone or in combination, do not suggest the methods claimed, let alone suggest that the claimed methods could be conducted with a reasonable expectation of success.

First, Applicants note that claim 14 has been amended herein to include a new step (iv), which recites that the sorting step (iii) is repeated on the single stranded nucleic acids isolated in step (h). Applicants bring the Examiner's attention to pages 5 and 8 of the present specification, which, along with the teaching of the application as a whole, show that a different set of oligonucleotide sequences which recognize a further portion of the nucleic acid sequence (which was double stranded after digestion with endonuclease) are used in this further sorting step. Specifically, page 8 discloses the use of primers "which overlap further into the unknown sequence".

Turning now to the outstanding rejections and cited references, Applicants submit that the cited references do not teach or suggest the claimed invention. The method of the presently claimed invention is directed to physically sorting nucleic acids, in order to allow for a reduction in the complexity of a nucleic acid population (*see* page 1, paragraph 1, of the present specification). In contrast, the method disclosed by Rothberg is directed to identifying/classifying and quantifying DNA sequences. Although it may appear subtle, there is a significant difference between the "sorting" of the present invention and "identifying/classifying" DNA, as cited in Rothberg. Specifically, "sorting" refers to the physical separation of samples/ groups of samples of DNA within a DNA population. In contrast, identifying/classifying, as disclosed in Rothberg, refers to the mere analysis of a given DNA population, in order to elucidate quantitative information about the DNA sequences within the population. Thus, there is a clear difference between physically separating the components of a mixture, as in the present invention, and merely determining what is in the mixture, as disclosed in the cited reference.

Thus, the skilled artisan, when presented with the problem of sorting a complex DNA population into more manageable sub-populations, would not have consulted Rothberg, because Rothberg does not apply to or cover the physically sorting of nucleic acids.

Furthermore, claim 14, as amended herein, recites the repetition of the sorting process to further sort the nucleic acids which are isolated in step (h). Neither Rothberg nor Dynal disclose, or even suggest, repeating the method or the further sorting of the nucleic acid population. In fact, the method disclosed in Rothberg would not permit further

sorting. This is because the results which would be achieved by repeating the process of amplification with the method of Rothberg, using different primers but without immobilization, would be unpredictable, as the original nucleic acid population, as well as the amplification products would remain in the sample mixture.

Applicants further submit that the skilled artisan would not have combined the teachings of Rothberg and Dynal. In fact, Rothberg actively teaches away from applying the method of Dynal. Applicants refer the Examiner to column 50, lines 5-8, of Rothberg, which the Office Action cites in saying "following the RE/ligase step is amplification of the doubly cut cDNA fragments such that any amplification method that selects fragments to be amplified based on end sequences is adaptable". It appears that the Office Action uses this statement as a basis for applying the "amplification method" of Dynal to the method of Rothberg. However, Applicants note that the amplification step disclosed in Rothberg is merely necessary to detect (and/or quantitate) a given DNA sequence. It is clearly not intended to be used as a sorting step. This argument is supported by the statement on lines 8-12 of column 50, directly following the passage in question, which states that "With high enough sensitivity of detection means, or even single molecule detection means, the amplification step can be dispensed with entirely. This is preferable as amplification inevitably distorts the quantitative response of the method". Accordingly, this passage actively leads the skilled artisan away from applying Dynal to Rothberg, because an amplification step is clearly not preferred. Thus, Dynal does not disclose an amplification method.

Finally, Applicants submit that the advantages of the claimed invention flow from the particular combination of extension and immobilization steps, and the order in which they are performed. As they fail to disclose the claimed steps and order of performance, these advantages clearly do not flow from the combination of Rothberg and Dynal. Page 6 of the Office Action states that "the ordinary artisan would have been motivated to have performed the categorizing method of Rothberg and subsequently performed the method of Dynal to synthesize single stranded probes [which were] identified by the categorization method of Rothberg". Thus, the Office Action appears to be stating that the method of the claimed invention (without the feature that the oligonucleotides are covalently linked to a solid support) can be performed by simply annexing these two cited references. However, in light of the above remarks, Applicants submit that the skilled artisan could not arrive at the claimed invention simply by reviewing the cited references. As Van Ness and Hartley merely disclose that covalently immobilized capture nucleic acid sequences have certain improved properties over non-covalently attached capture nucleic acids, and non-standard bases, respectively, these references fail to remedy the deficiencies of Rothberg, as well as Dynal.

Thus, the references, when considered alone or in combination do not render obvious the invention as claimed. Accordingly, Applicants respectfully request the appropriate withdrawal of the rejection.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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14. (Thrice Amended) A method for sorting [categorizing] nucleic acid, wherein said method comprises:

(i) digesting double-stranded nucleic acid with an endonuclease to produce a nucleic acid population, wherein said endonuclease is selected such that each nucleic acid in the resulting nucleic acid population has a sticky end of a known base sequence and of a known common length extending from a terminal of its double-stranded portion, and wherein each nucleic acid in the nucleic acid population has a double-stranded portion;

(ii) contacting the nucleic acid population with an adaptor to ligate the adaptor to a terminal of each nucleic acid in the nucleic acid population, wherein said adaptor comprises a double-stranded primer portion having a known base sequence, and a single-stranded portion complementary to the known sticky end of the nucleic acids in the nucleic acid population;

(iii) categorizing the nucleic acid by isolating nucleic acids wherein both termini of the double-stranded portion of said nucleic acid correctly hybridize to an oligonucleotide sequence by contacting a first set of oligonucleotide sequences with the nucleic acid population by:

(a) denaturing the nucleic acid population in the presence of the first set of oligonucleotide sequences covalently linked to a solid phase support to produce a single-stranded nucleic acid population and allowing the single-stranded nucleic acid to hybridise to the first set of oligonucleotide sequences, wherein each oligonucleotide sequence in said

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first set of oligonucleotide sequences has a pre-determined recognition sequence, the nucleic acid being categorized by its ability to correctly hybridize to oligonucleotide sequences having the recognition sequence, the recognition sequence being situated such that it recognizes a sequence in the portion of the nucleic acid which was double-stranded after digestion with the endonuclease;

(b) immobilizing those nucleic acids which correctly hybridise to the oligonucleotide sequence added to that well;

(c) extending the correctly hybridised oligonucleotide sequences along the single-stranded portion of the immobilised nucleic acid to form double-stranded nucleic acid;

(d) denaturing the double-stranded nucleic acid and removing non-immobilised species to isolate the resulting immobilised single-stranded nucleic acid;

(e) contacting the immobilised single-stranded nucleic acid with a second set of oligonucleotide sequences, wherein each oligonucleotide sequence in said second set of oligonucleotide sequences has a pre-determined recognition sequence, the nucleic acid being categorized by its ability to correctly hybridize to oligonucleotide sequences having the recognition sequence, the recognition sequence being situated such that it recognizes a sequence in the portion of the nucleic acid which was double-stranded after digestion with the endonuclease;

(f) extending the correctly hybridised oligonucleotide sequences along the immobilised single-stranded nucleic acid to form double-stranded nucleic acid;

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(g) denaturing the double-stranded nucleic acid; and

(h) isolating the resulting non-immobilised single-stranded nucleic acid; and

(iv) further sorting the isolated single stranded nucleic acid of step (h) by repeating step (iii) on the isolated single stranded nucleic acid of step (h), wherein the first set of oligonucleotide sequences is replaced by a third set of oligonucleotide sequences, each oligonucleotide sequence of the third set recognizing a further portion of the nucleic acid which was double stranded after digestion with the endonuclease, and wherein the second set of oligonucleotide sequences is replaced by a fourth set of oligonucleotide sequences , each oligonucleotide sequence of the fourth set recognizing a further portion of the nucleic acid which was double stranded after digestion with the endonuclease.